INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

PRIORITY DOCUMENT

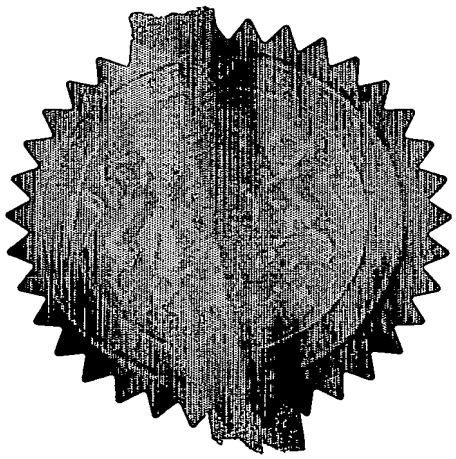
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

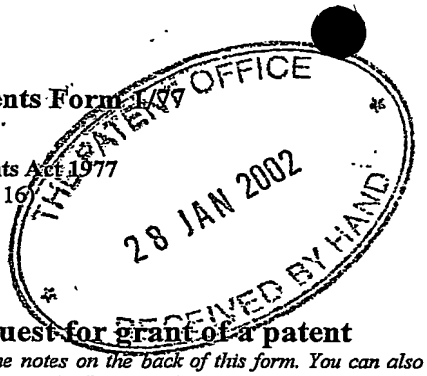


Signed P. Mahoney

Dated 24 January 2003

Patents Form 1/77

Patents Act 1977
(Rule 16)



The **Patent Office**

1/77

29JAN02 E691344-1 000524
P01/7700 0.00-0201882.8
The Patent Office
Cardiff Road
Newport
Gwent NP10 8QQ

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

1.	Your reference	4-32326P1
2.	0201882.8	28 JAN 2002
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	7125487005
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	Organic Compounds
5.	Name of your agent *(If you have one)*	
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH
	Patents ADP number *(if you know it)*	1800001

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*	Yes
	a) any applicant named in part 3 is not an inventor, or	
	b) there is an inventor who is not named as an applicant, or	
	c) any named applicant is a corporate body.	
	(see note (d))	

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	11
Claim(s)	6
Abstract	1
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	ONE
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature Date

B.A. Yorke & Co.

B.A. Yorke & Co. 28 January 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. E. Cheetham
020 8560 5847

Warning

After an application for a patent has been filed. the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the united Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) Once you have filled in the form you must remember to sign and date it.

e) For details of the fee and ways to pay please contact the Patent Office.

Organic Compounds

The invention relates to the use of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide (hereinafter: "COMPOUND I") or a pharmaceutically acceptable salt thereof for the manufacture of pharmaceutical compositions for use in the treatment of inflammatory diseases especially rheumatoid arthritis (RA), to the use of COMPOUND I or a pharmaceutically acceptable salt thereof in the treatment of inflammatory diseases especially RA, to a method of treating warm-blooded animals including mammals, especially humans suffering from or susceptible to inflammatory disease especially RA by administering to a said animal in need of such treatment an effective dose of COMPOUND I or a pharmaceutically acceptable salt thereof.

The invention also relates to a combination of COMPOUND I or a pharmaceutically acceptable salt thereof with one or more disease modifying arthritis rheumatoid drugs (DMARDs) to treat warm-blooded animals including mammals, especially humans having or susceptible to inflammatory diseases especially rheumatoid arthritis.

The monomethanesulfonic acid addition salt of COMPOUND I (hereinafter "SALT I") and a preferred crystal form thereof are described in PCT patent application WO99/03854 published on January 28, 1999.

Rheumatoid Arthritis (RA) is a common chronic debilitating disease that may affect the longevity of life. The clinical course of RA is variable but it has become clear that the outcome of rheumatoid arthritis is much worse than was previously thought. The range of presentation of RA is broad but the disease onset is insidious in most cases and the first symptoms are pain, swelling and stiffness in the joints. The characteristic feature of RA is persistent inflammatory peripheral arthritis but also various extra-joint manifestations may be seen such as rheumatoid nodules, vasculitis, pulmonary fibrosis, neurological manifestations and Felty's syndrome. RA causes the loss of joint motility and can make accomplishing simple task difficult. If the persistent inflammation has led into the development of secondary amyloidosis involving kidneys, it has been estimated that the life expectancy is only about 4-5 years. RA has a substantial social effect in terms of cost, disability lost of quality of life and lost productivity. RA affects about 1% of the population in a female/male ration of 3/1. Only in the United States, about two million people suffer from RA. The disease can occur at any

age but about 80% of people with RA are diagnosed between ages 35-50 and its incidence is increasing with age. The lack of test that can absolutely diagnose RA leads to a several month delay before a firm diagnosis of RA can be ascertained.

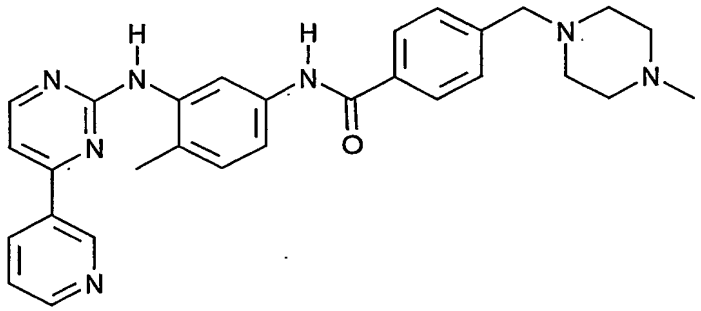
Management of RA is a major problem since there is no cure available. Therapeutic options for RA include disease modifying anti-rheumatic drugs (DMARDs). DMARDs improved inflammatory symptoms or slowed progression of joint erosions however they were often only partly effective and poorly tolerated in long-term therapy. All of the DMARDs have significant toxic side effects, which require healthcare professionals to carefully compare the risks associated with these medications versus the benefits. The methotrexate doses used in treatment of RA are small (7 to 20 mg once weekly), but they may sometimes be associated with severe adverse effects, such as hepatic fibrosis or pneumonitis. Despite 50 to 80 % of the patients undergoing the methotrexate treatment have long-term stabilization of functional status, durable remissions have never been reported. Moreover, severe RA is often treated with doses at the expense of toxicity and the response may be inadequate. Among the newly approved drugs for the treatment of RA, the so-called anti-Tumor Necrosis Factor (TNF) α therapy (infliximab and etarnecept) has shown to be very effective however, approximately 30-40 % of patients do not respond even to this therapy. The cyclooxygenase (COX)-2 inhibitor (celecoxib) has a similar efficacy to classical DMARDs and a comparable safety profile but it favors cardiovascular events in patients at risk and it must be used also with caution in patients with ulcer history and in the elderly.

It has now surprisingly been demonstrated that inflammatory diseases, especially RA can be successfully treated with COMPOUND I or pharmaceutically acceptable salt thereof.

Two major rat models in rheumatoid arthritis have contributed to the understanding of RA and have yielded promising new approaches to treatment. Surprisingly in both models of induced RA, SALT I showed significant inhibition of the induced swelling up to 42 %. Adjuvant arthritis in the rat is one of the most commonly used models for evaluating anti-arthritic drugs (see Billingham, M.E., Pharmacol. Ther. 21: 389-428 (1983)). A chronic polyarthritis develops in several joints after the intradermal injection of complete Freunds adjuvant). Rat with adjuvant arthritis treated from day 15 at a dose of 100 mg/kg/day of SALT I per day exhibited a significant paw swelling inhibition.

In the antigen-induced rheumatoid arthritis model (Dumonde, D.C. and Glynne, L.E. Br. J. Exp. Pathol. 43: 373-383 (1962)), the inhibition was even greater (42%) at a lower dose (30 mg/kg/day) of SALT I.

COMPOUND I is 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide having the formula I



(I)

The invention thus relates to the preparation of COMPOUND I and the use thereof, as an anti-inflammatory agent especially as an anti-rheumatoid arthritis agent.

Pharmaceutically acceptable salts of COMPOUND I are pharmaceutically acceptable acid addition salts, like for example with inorganic acids, such as hydrochloric acid, sulfuric acid or a phosphoric acid, or with suitable organic carboxylic or sulfonic acids, for example aliphatic mono- or di-carboxylic acids, such as trifluoroacetic acid, acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, fumaric acid, hydroxymaleic acid, malic acid, tartaric acid, citric acid or oxalic acid, or amino acids such as arginine or lysine, aromatic carboxylic acids, such as benzoic acid, 2-phenoxy-benzoic acid, 2-acetoxy-benzoic acid, salicylic acid, 4-aminosalicylic acid, aromatic-aliphatic carboxylic acids, such as mandelic acid or cinnamic acid, heteroaromatic carboxylic acids, such as nicotinic acid or isonicotinic acid, aliphatic sulfonic acids, such as methane-, ethane- or 2-hydroxyethane-sulfonic acid, or aromatic sulfonic acids, for example benzene-, p-toluene- or naphthalene-2-sulfonic acid.

Depending on species, age, individual condition, mode of administration, and the clinical picture in question, effective doses, for example daily doses of about 100-1000 mg, preferably 200-600 mg, especially 400 mg, are administered to warm-blooded animals of about 70 kg bodyweight. For adult patients with inflammatory diseases, especially rheumatoid arthritis, a starting dose of 400 mg daily can be recommended. For patients with

an inadequate response after an assessment of response to therapy with 400 mg daily, dose escalation can be safely considered and patients may be treated as long as they benefit from treatment and in the absence of limiting toxicities.

The invention relates also to a method for administering to a human subject suffering from an inflammatory disease, especially rheumatoid arthritis, COMPOUND I or a pharmaceutically acceptable salt thereof, which comprises administering a pharmaceutically effective amount of COMPOUND I or a pharmaceutically acceptable salt thereof to the human subject once daily for a period exceeding 3 months. The invention relates especially to such method wherein a daily dose of 200 to 800 mg, especially 400-600 mg, preferably 400 mg, of SALT I is administered.

The invention also relates in a combination which comprises (a) COMPOUND I or a pharmaceutically acceptable salt thereof and (b) a therapeutic agent selected from the anti-rheumatoid arthritis drugs, most preferably a combination wherein the combination partners are present in synergistically effective amounts.

Surprisingly, it has been found a synergistic effect of a combination as defined herein as its anti-rheumatoid effect is greater than the effects that can be achieved with either type of combination partner alone, i.e. greater than the effects of a monotherapy using only one of the combination partners as defined herein. All the more surprising is the finding that the administration of SALT I in combination with another anti-rheumatoid drug, especially prednisone, results in a surprising beneficial effect that a lower dose of the active compounds in combination can be used. This is in accordance with the desires and requirements of the patients to be treated.

The anti-rheumatoid arthritis drug (DMARD) can be, but is not limited to, one or more of the following (most of them are commercially available):
(1) actarit, allocupreide sodium, bucillamine, celecoxib, clobuzarit, cuproxoline, diacerein, glucosamine, kebuzone, lobenzarit, melittin, myoral, methotrexate, leflunomide, cyclosporine, sulfasalazine, azathioprine, penicillamine, chlorambucil, cyclophosphamide, minocycline
(2) a non steroidal anti-inflammatory drug (NSAID) such as acetylsalicylic, ibuprofen, diclofenac, celecoxib, tenoxicam or naproxen

(3) an anti-inflammatory steroidal drug such as 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clobetasone, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difluprednate, enoxolone, fluazacort, flucloronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halometasone, halopredone acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, maziprednone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylamino acetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, triamcinolone hexacetonide
(4) a gold salt such as gold sodium thiomalate, aurothioglycanide, calcium 3-aurothio-2-propanol-1-sulfonate, aurothioglucose, auranofin
(5) anti-malarial drugs such as chloroquine, hydroxychloroquine,
(6) angiogenesis inhibitors, monoclonal antibodies to adhesion molecules and growth factors, ICE inhibitors, 5-HT_3 receptor antagonists e.g. tropisetrone, p38 mitogen activated protein kinase inhibitors, matrix metalloproteinase inhibitors, lymphokine antagonists such as IL-1 receptor antagonists or anti-tumor necrosis factor α agents e.g. etanercept, infliximab.

The effective dosage of each of the combination partners employed in the combination may vary depending on a variety of factors including the particular combination of the pharmaceutical compound partners, the route of administration, the severity of the disease, the renal and hepatic functions of the patient. The molar ratio (a)/(b) of the combination partners is about 0.1 to 10, most preferably 0.3 to 3 and the unit dosage form contains 20 to 200 mg, most preferably 50 to 150 mg of the monomethanesulfonate salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide of the formula I.
A patient that had suffered severe RA for 30 years, her joint movements were severely limited due to the persistence of the disease. She was treated with prednisone (5 mg/day) and SALT I orally at the dose of 600 then 400 mg/day. After several days of the treatment, she already reported improved general condition like improved joint motility and decrease of wrist swelling. After 2 and 5 months of treatment, further major improvements were noticed.

Importantly, the clinical toxicity profile of oral SALT I therapy was shown to be remarkably favorable, in other therapy, SALT I is relatively low toxic, and its safety profile might rival those of methotrexate or gold preparations.

Example 1: Therapeutic Dosing of SALT I in the rat Adjuvant Arthritis Model

Female Wistar rats weighting 150-170g (housed in standard conditions, 5 animals per cage, with food and water *ad libitum*) are injected intra dermaly at the base of the tail with 0.1 ml of mineral oil containing 0.6 mg of lyophilised heat-killed *Mycobacterium tuberculosis* (Complete Freund Adjuvant). The rats are treated with COX-2 inhibitor (0.5 mg/kg per os q.d.) or vehicle (water) or with SALT I (10, 30 or 100 mg/kg per os q.d.) from day 15 to day 22. At the end of the experiment, the swelling of the tarsal joints is measured by means of a micro-calliper. Percentage inhibition of paw swelling is calculated by reference to vehicle treated arthritic animals (0 % inhibition) and vehicle treated normal animals (100 % inhibition).

Table 1. Inhibition of paw swelling by SALT I in the rat adjuvant arthritis model

Experiment no.	**% inhibition (mean±sem)**
Control compound (COX-2 inhibitor)	52.9±7.0
SALT I 10	-2.7±5.5
SALT I 30	-4.9±4.8
SALT I 100	27.8±5.3

COX-2 was administered at 0.5 mg/kg p.o. q.d for 7 days starting from Day 15. Arthritis normally appears on Day 11 or 12. Values are mean ± s.e.m., n = 5.
SALT I shows a significant inhibition of paw swelling at the dose of 100 mg/kg/day.

Example 2: Prophylactic Dosing of SALT I in the rat Adjuvant Arthritis Model

Female Wistar rats weighting 150-170g (housed in standard conditions, 5 animals per cage, with food and water *ad libitum*) are injected intradermally at the base of the tail with 0.1 ml of mineral oil containing 0.6 mg of lyophilised heat-killed *Mycobacterium tuberculosis*. The rats are treated with COX-2 inhibitor (0.5 mg/kg p.o. q.d.) or vehicle (water) or with SALT I (10, 30 or 100 mg/kg p.o. q.d.) from the time of immunization. At the end of the experiment, the swelling of the tarsal joints is measured by means of a micro-calliper. Percentage inhibition

of paw swelling is calculated by reference to vehicle treated arthritic animals (0 % inhibition) and vehicle treated normal animals (100 % inhibition).
It is to expect that SALT I is much more active in the Adjuvant Rheumatoid Arthritis if given prophyllactically as it has been reported for COX-2 inhibitor.

Example 3: The rat Antigen-Induced Arthritis Model

Lewis rats (female) are injected intradermally on days -21 and -14 with methylated Bovine Serum Albumin (mBSA) homogenised 1:1 with complete Freunds adjuvant. On day 0, the animals receive an intra-articular injection of mBSA in 5% glucose solution into the right knee, the left knee receiving 5% glucose solution vehicle alone. SALT I is dosed from the day of arthritis induction up to day 14. Arthritis is assessed by measuring the diameters of both knees in the medial-lateral direction and expressed as a ratio of the right knee diameter/left knee diameter. Control arthritic animals are included in all experiments, and treated with the drug vehicle solution alone. COX-II inhibitor is used as a drug control in all experiments.
Table 2. Inhibition of knee swelling by SALT I in the rat antigen-induced arthritis model

Experiment no.	**% inhibition (mean±sem)**
Control compound (COX-2 inhibitor)	64.5±5.0
SALT I 10	29.7±7.3
SALT I 30	42.0±6.7
SALT I 100	38.5±2.3

COX-2 was administered at 0.5 mg/kg p.o. q.d.Values are mean ± s.e.m., n = 5.
The paw swelling inhibition is significant compared to the control at the dose of 10 mg/kg/day and a 42% inhibition is obtained at the dose of 30 mg/kg/day. Since significant inhibition is achieved at all SALT I doses, this result suggest that higher doses are not be more effective on the knee swelling parameter.

Example 4: Findings in a single patient with severe RA treated with SALT I

We treated a patient who had concomitant rheumatoid arthritis and metastatic gastrointestinal tumor to the liver with SALT I 600 mg daily. The patient had suffered from RA for about 30 years, and the disease had previously been treated with multiple therapies, including gold preparations, methotrexate, NSAIDs, prednisone, and corrective surgery of the toes, feet, and wrists. The patient was diagnosed with mesangial glomerulonephritis in 1988, and she also had the diagnoses of hypertension and Crohn's disease (ileitis

terminalis). Her joint movements were severely limited due to persistent RA, but she was able to walk without walking aids. Nine days after starting SALT I (started on March 21, 2001) she developed nausea, anuria and paralytic ileus, which were considered to related with SALT I. SALT I was discontinued, and the kidney function returned rapidly to normal with intravenous hydration. No obstructing tumors were found in the abdomen in CT or in passage X-ray, and the cessation of bowel movements was assumed to result from the inhibitory effects of SALT I on the bowel movements. The bowel movements returned with conservative treatment, and SALT I was resumed at the dose of 400 mg on April 11. On a control visit on April 17 the patient reported improved general condition. Interestingly, she reported improved joint motility and decreased swelling particularly in the wrists, suggesting decreased activity of RA. On June 14, 2001 the patient reported further subjective improvement of her RA. For example, she was now able to comb her hair, which she was formerly unable to do due to substantially restricted shoulder movements. The upright position of her left great toe had become horizontal probably due to decrease in size of a rheumatic nodule, her wrist oedema had subsided and the wrist movements were improved. Interestingly, her occasional macroscopic hematuria had ceased suggesting improvement in RA-associated glomerulonephritis. These changes occurred despite the patient had reduced her antirheumatic medication. She had been taking prednisone 10 mg p.o. q.i.d. and ibuprofein 600 mg t.i.d as her anti-RA medication, but ibuprofein had been discontinued on April 4 because of the renal problems, and the patient had reduced the prednisone dose to 5 mg o.d. Her GIST was responding with about 40% reduction in the tumor volume. In September 2001, both her RA and GIST are still in remission.

Example 5: Clinical Trials

Three patients suffering from severe rheumatoid arthritis according to the revised American College of Rheumatology Criteria (ACR, 1987) will be treated in this proof-of-concept study.

STUDY MEDICATION

The study drug SALT I is added on the anti-rheumatic medication which the patient is taking at the onset of the study. However, those anti-rheumatic drugs which can be suspected to have drug interactions with SALT I are discontinued before the beginning of the study. The starting dose of the drug will be 200 mg once daily. If no severe adverse events (grade 3 or 4 according to the NCI toxicity criteria) occur the dose of SALT I will be increased to 300 mg at the beginning of the study week three and then to 400 mg once per day in the beginning

of week 5, which dose is used until the end of the study unless grade 3 or 4 toxicity is encountered. If grade 3 or 4 toxicity occurs at the dose level 400 mg/day, the study medication is withheld until grade 1 or less, and then resumed at the dose of 300 mg/day, and if such toxicity occurs at the dose level 300 mg/day, SALT I is resumed at the dose of 200 mg/day. If grade 3 or 4 toxicity occurs at the dose of 200 mg/day, the patient is removed from the study.

No changes in the doses of concurrent corticosteroids, non-steroidal anti-inflammatory drugs or DMARDs is made during SALT I medication unless the disease progresses or unless medically necessary. Intra-articular corticosteroid injections are allowed during the study if clinically indicated.

VISIT SCHEDULE

The study is planned to last 12 weeks. During that time the patients have a screening visit (baseline) and a total of 4 follow-up visits (weeks 2, 4, 8, and 12). On each visit complete physical check up is performed (including blood pressure, pulse, body weight) and the following parameters will be assessed:

1) The number of swollen joints (in a 66 joint count)
2) The number of tender joints (in a 66 joint count)
3) VAS (visual analog pain scale)
4) The patient global assessment of disease activity
5) The doctor's global assessment of disease activity
6) HAQ (health assessment questionnaire) (weeks 0, 2, 8, 12)
7) Histological assessment of synovia from a biopsy (optional)
8) Concomitant medications
9) Adverse effects (the patients will use a diary)

Blood tests: At baseline (d. –7 to 0) and on each visit (visits 1 to 4) blood tests will be taken:

A. hematologogy: hemoglobin, total WBC count, a differential count including neutrophils, lymphocytes, monocytes, eosinophils and basophils

B. blood chemistry: creatinine, uric acid, albumin, total protein, total bilirubin, alkaline phophatase, AST, ALT, LDH

C. CRP, ESR and urine analysis

D. rheumatoid factor and immunoglobulins will be assessed at baseline and at 4-, 8- and 12-week visits

During the first 4 weeks of the study blood tests (A to C above) are taken weekly and during the second month of the study (weeks 4 to 8) biweekly to monitor drug safety.

Research blood samples are collected as at baseline, and at the 4- and 12-week visits. These is used to monitor the pro-inflammatory and anti-inflammatory cytokine levels before and during the treatment (IL-2, -6, -10, -12, TNF-alpha, SCF).

An X-ray of the hands is taken before starting SALT I (d. –7 to 0) and after 12 weeks of treatment (visit 4).

Synovial fluid aspiration. If the patient has synovitis in the knee joint which requires synovial fluid aspiration samples are be taken from the synovial fluid to determine the SCF level, mast cell tryptase level, and the activity of the synovial fluid matrix metalloproteinases.

A synovia biopsy may be taken at baseline within 2 weeks before starting SALT I, and repeated 2 to 3 months after enrollment (optional).

Example 6: Capsules with 4-[(4-methyl-1-piperazin-1-ylmethyl)-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide methanesulfonate, β-crystal form

Capsules containing 119.5 mg of the compound named in the title (= SALT I) corresponding to 100 mg of COMPOUND I (free base) as active substance are prepared in the following composition:

Composition	
SALT I	119.5 mg
Cellulose MK GR	92 mg
Crospovidone XL	15 mg
Aerosil 200	2 mg
Magnesium stearate	1.5 mg
	230 mg

The capsules are prepared by mixing the components and filling the mixture into hard gelatin capsules, size 1.

Example 7: Capsules with 4-[(4-methyl-1-piperazin-1-ylmethyl)-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide methanesulfonate, β-crystal form

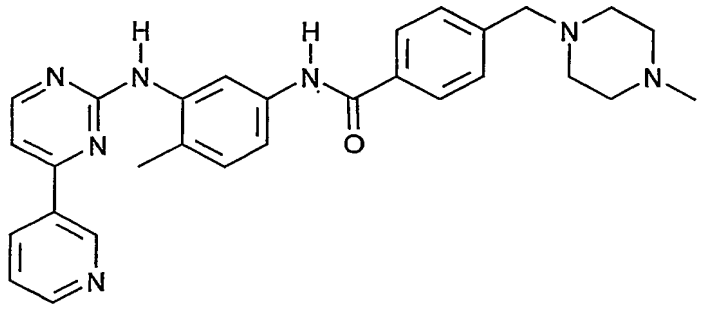
Capsules containing 100 mg of the compound named in the title (= SALT I) as active substance are prepared in the following composition:

Composition	
Active substance	100 mg
Avicel	200 mg
PVPPXL	15 mg
Aerosil	2 mg
Magnesium stearate	1.5 mg
	318.5 mg

The capsules are prepared by mixing the components and filling the mixture into hard gelatin capsules, size 1.

Claims:

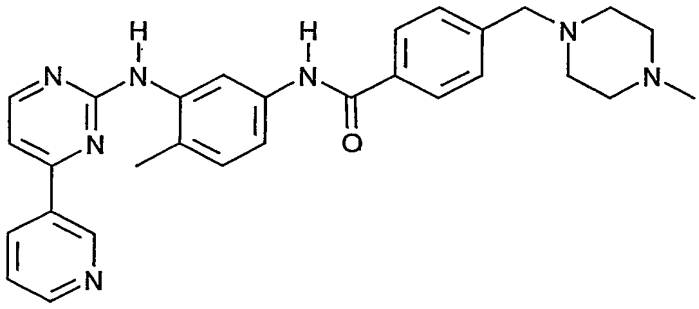
1. The use of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-yl-amino)phenyl]-benzamide of the formula I



(I)

or a pharmaceutically acceptable salt thereof for the manufacture of pharmaceutical compositions for use in the treatment of inflammatory diseases.

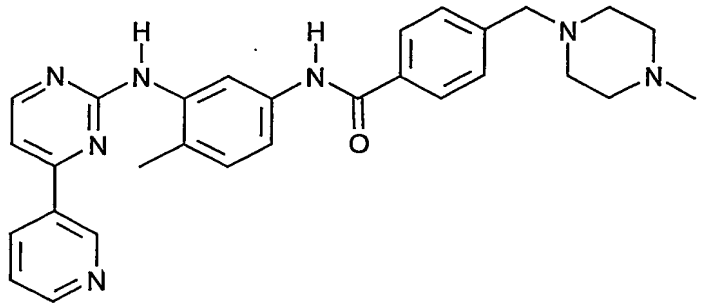
2. The use of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-yl-amino)phenyl]-benzamide of the formula I



(I)

or a pharmaceutically acceptable salt thereof in the treatment of inflammatory diseases.

3. A method of treating humans suffering from an inflammatory disease which comprises administering to a said human in need of such treatment an anti-inflammatorily effective dose of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-yl-amino)phenyl]-benzamide of the formula I



(I)

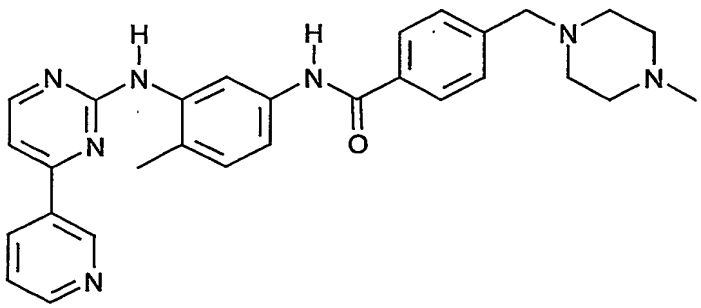
or a pharmaceutically acceptable salt thereof.

4. Use or method according to claim 3 wherein a pharmaceutically acceptable acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-yl-amino)phenyl]-benzamide of the formula I is administered.

5. Use or method according to claim 3 wherein the monomethanesulfonate salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide of the formula I is administered.

6. Use or method according to claim 3 wherein a daily dose of 200 to 800 mg of a monomethanesulfonate salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide of the formula I is administered to an adult human.

7. A method for treating to a mammal subject suffering from an inflammatory disease 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide of the formula I



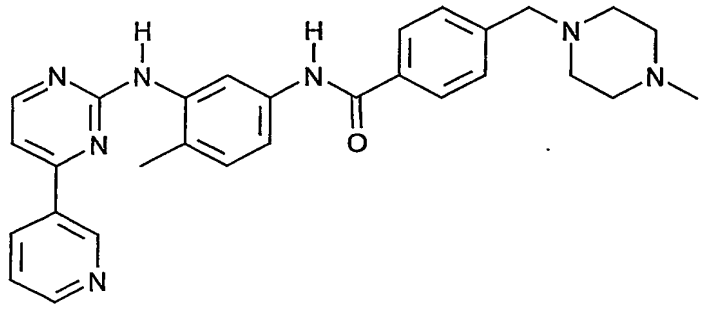
(I)

or a pharmaceutically acceptable salt thereof, which comprises administering a pharmaceutically effective amount of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide of the formula I or a pharmaceutically acceptable salt thereof to the human subject once daily for a period exceeding 3 months.

8. A method according to claim 7 wherein a daily dose of 200 to 600 mg of the monomethanesulfonate salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide of the formula I is administered to a human.

9. Use or method according to any one of claims 1 – 8 wherein the inflammatory disease is rheumatoid arthritis.

10. A method of treating mammals suffering from rheumatoid arthritis which comprises administering to a said mammal in need of such treatment a pharmaceutical composition comprising
(a) a dose, effective against rheumatoid arthritis, of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide of the formula I



(I)

or a pharmaceutically acceptable salt thereof and
(b) a therapeutically effective amount of a second drug selected from the disease modifying arthritis rheumatoid drugs (DMARDs).

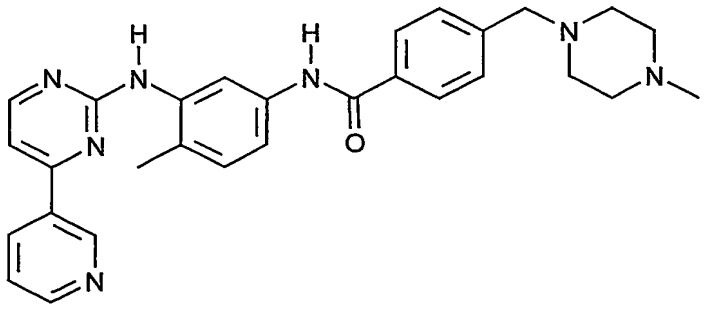
11. A method according to claim 10 wherein the second drug (b) is a non-steroidal anti-inflammatory drug and the mammal is a human.

12. A method according to claim 10 or 11 wherein the second drug (b) is selected from the group consisting of actarit, allocupreide sodium, bucillamine, celecoxib, clobuzarit,

cuproxoline, diacerein, glucosamine, kebuzone, lobenzarit, melittin, myoral, methotrexate, leflunomide, cyclosporine, sulfasalazine, azathioprine, penicillamine, chlorambucil, cyclophosphamide, minocycline, acetylsalicylic, ibuprofen, diclofenac, celecoxib, tenoxicam or naproxen, 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clobetasone, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difluprednate, enoxolone, fluazacort, flucloronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halometasone, halopredone acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, maziprednone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylamino acetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, triamcinolone hexacetonide, gold sodium thiomalate, aurothioglycanide, calcium 3-aurothio-2-propanol-1-sulfonate, aurothioglucose, auranofin, chloroquine, hydroxychloroquine, angiogenesis inhibitors, monoclonal antibodies to adhesion molecules and growth factors, IL-1β converting enzyme inhibitors, 5-HT_3 receptor antagonists e.g. tropisetrone, p38 mitogen activated protein kinase inhibitors, matrix metalloproteinase inhibitors and lymphokine antagonists such as IL-1 receptor antagonists or anti-tumor necrosis factor α agents e.g. etanercept, infliximab.

13. A combination which comprises

(a) 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-yl-amino)phenyl]-benzamide of the formula I



(I)

or a pharmaceutically acceptable salt thereof and
(b) a disease modifying arthritis rheumatoid drug (DMARD) selected from the group consisting of actarit, allocupreide sodium, bucillamine, celecoxib, clobuzarit, cuproxoline, diacerein, glucosamine, kebuzone, lobenzarit, melittin, myoral, sulfasalazine, penicillamine, chlorambucil, minocycline, acetylsalicylic, ibuprofen, diclofenac, celecoxib, tenoxicam or naproxen, 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clobetasone, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difluprednate, enoxolone, fluazacort, flucloronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halometasone, halopredone acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, maziprednone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylamino acetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, triamcinolone hexacetonide, gold sodium thiomalate, aurothioglycanide, calcium 3-aurothio-2-propanol-1-sulfonate, aurothioglucose, auranofin, chloroquine, hydroxychloroquine, monoclonal antibodies to adhesion molecules and growth factors, IL-1β converting enzyme inhibitors, 5-HT_3 receptor antagonists e.g. tropisetrone, p38 mitogen activated protein kinase inhibitors, matrix metalloproteinase inhibitors and lymphokine antagonists such as IL-1 receptor antagonists or anti-tumor necrosis factor α agents e.g. etanercept, infliximab.

14. A combination according to claim 13 wherein the combination partners are present in synergistically effective amounts.

15. A combination according to claim 14 wherein the molar ratio (a)/(b) of the combination partners is between 0.1 to 10.

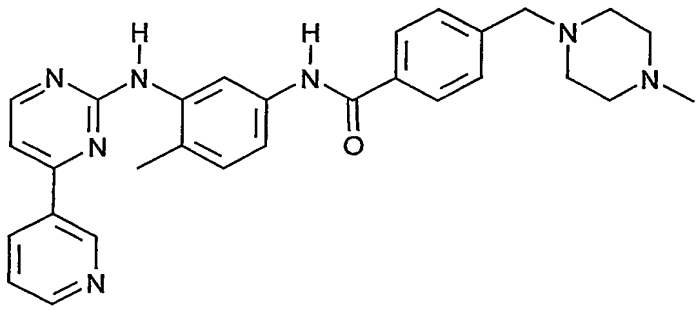
16. A combination according to claim 15 wherein the molar ratio is between 0.3 to 3.

17. A combination according to claim 15 or 16 wherein a unit dosage form contains 20 to 200 mg of the monomethanesulfonate salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide of the formula I.

18. A combination according to claim 17 wherein a unit dosage form contains 50 to 150 mg of the monomethanesulfonate salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide of the formula I.

Abstract

4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide of the formula I



(I)

or a pharmaceutically acceptable salt thereof can be used in the treatment of inflammatory diseases, especially rheumatoid arthritis. The invention also relates to a combination of the compound of the formula I or a pharmaceutically acceptable salt thereof with one or more disease modifying arthritis rheumatoid drugs (DMARDs).